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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

28 SEP 2004

Applicant's or agent's file reference P33637WO/KVC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 03/01112	International filing date *(day/month/year)* 17.03.2003	Priority date *(day/month/year)* 28.03.2002
International Patent Classification (IPC) or both national classification and IPC C07D471/04, C07D471/04		
Applicant EISAI LONDON RESEARCH LABORATORIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.10.2003	17.03.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Weisbrod, T Telephone No. +49 89 2399-8931

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/01112

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-42 as originally filed

Claims, Numbers

1-63 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1 (part), 17 (part), 41-49,61-63

   because:

   ☒ the said international application, or the said claims Nos. 41-49,61-63 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1,17 (all part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-63
	No:	Claims	
Inventive step (IS)	Yes:	Claims	16
	No:	Claims	1-15,17-63
Industrial applicability (IA)	Yes:	Claims	1-40,50-60
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item I
Basis of the opinion

The application is directed to
(i) 7-azaindoles (I) (claims 1-16),
(ii) a prodrug of such compound (I) (claims 17),
(iii) a process for preparing compounds (I) (claims 18-27),
(iv) a pharmaceutical composition comprising compounds (I) (claims 28-30),
(v) a process for preparing such composition (claim 31),
(vi) a compound (I) or the respective composition for use in therapy (claims 32-40),
(vii) the corresponding methods for the treatment of the human/animal body (claims 41-49 and 61-63),
(viii) the use of compounds (I) for manufacturing a medicament (claims 50-57), and
(ix) an assay for determining the activity of a compound (I) (claims 58-60).

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 Claims 41-49 and 61-63 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2 The ISA has not issued a search report for the claims 1 and 17, insofar as the expressions "pharmaceutically acceptable biohydrolyzable derivatives", "affinity reagents" and "prodrugs" are concerned (cf. search report).

For such partially searched claims it is not possible to determine whether, and if so to what extend, the matter to which said claims relate is novel and might involve an inventive step. No International Preliminary Examination will thus be carried out with regard to novelty and inventive step for subject-matter which is not covered by the search report (cf. Rule 66.1(e) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: WO 01/47922, 05.07.2001.
D2: WO 99/20624, 29.04.1999.
D3: WO 00/64872, 02.11.2000.
D4: Harper, S. J.; LoGrasso, P. *Drugs of the Future* **2001**, *26*, 957-973.

2 Novelty

D1 relates to azaindole derivatives as protein kinase inhibitors useful e.g. in the treatment of inflammatory diseases. The compounds of D1 generally comprise already certain present compounds (I) (cf. D1, claim 1, wherein X^1 is CH, R^1 and R^3 are aryl or heteroaryl, and R^2 is acyl) which are, however, not individualized in the said prior art. The present claimed compounds may thus be regarded as a novel selection of the compounds of D1.

D2 relates to antiinflammatory p-38 kinase inhibitors such as 2-(R^1)heteroaryl-3-(R^2)(aryl or heteroaryl)-5(R^6)heterocycloalkyl-4-azaindoles (cf. claim 1, item (ii) wherein P represents structure S; and pages 21-28 and 30-31). The present compounds (I) differ from the compounds of D2 through the position of the pyridine nitrogen and the 3-C(Z)XYR' substituent. The present claimed matter is thus novel in view of D2.

D3 discloses isatine derivatives as inhibitors of c-Jun N-terminal kinases (JNK's), from which the present compounds (I) differ through the additional ring nitrogen atom, the carbo- or heterocyclic group R (corresponding with R^2 in D3), and the presence of R" instead of the 2-oxo group of the compounds of D3. The present claimed matter is thus novel in view of D3.

D4 represents a review article on inhibitors of the JNK pathway. The document is not relevant to the question of novelty of the present application, because it does not disclose the present compounds (I).

In view of D1 to D4 the application complies with the criterion of novelty according to Article 33(2) PCT.

3 Inventive Step

3.1 The application describes the synthesis of certain compounds (I) and shows that three 5(R)-phenyl substituted compounds (I) represent inhibitors of JNK3 kinase.

3.2 In view of D3 and/or D4 as most relevant state of the art, the problem underlying the application is seen in the provision of further JNK3 kinase inhibitors. Due to the substantial structural differences between the present compounds and the compounds of the most relevant state of the art, it does not appear obvious that the skilled person whishing to provide further compounds of the desired activity would consider the present compounds as alternatives of the compounds of the said prior art. Consequently an inventive step may be acknowledged for the tested examples and plausible generalizations thereof i.e. the compounds of claim 16.

The applicant is, however, reminded that the breath of the claims should be such that it represents a reasonable generalization over the examples provided, and such that it is plausible that substantially all compounds falling within its scope of the claims actually provide a solution to the problem underlying the invention. In this context it is first of all noted that the terms such as "carbocyclyl", "heterocyclyl", "haloalkyl", "aryl", "heteroaryl", "alkyl", "optionally substituted aryl", "alkenyl", "alkynyl", "cycloalkyl", etc. used throughout the claims are open-ended and thus likely to comprise structures which will mot solve any relevant technical problem. Consequently, for compounds comprising such open-ended groups and for subject-matter referring to such compounds no inventive step would be acknowledged. The claims 1-15 and 17-63 lack thus an inventive step. Furthermore, merely based on the assay and its results according to the pages 40-42 of the application, no inventive step can be acknowledged for an assay for determining any activity whatsoever of the compounds (I) as defined in claim 58.

4 Industrial Applicability

For the assessment of the present claims 41-49 and 61-63 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5 Deficiencies of the Application under Article 5 and 6 PCT :

5.1 Present claim 58 relates to an assay for determining the activity of the compounds (I). The claim relates thus to an assay for determining any activity whatsoever of the compounds (I), whereas support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found only for an assay for determining the inhibitory potency against the kinases JNK1, JNK2, and JNK3. In the present case the said claim so lacks support and the application so lacks disclosure.

5.2 Claim 1 relates to compounds (I) as well as "pharmaceutically acceptable biohydrolyzable derivatives", "affinity reagents" or "prodrugs" thereof. Claim 17, furthermore, relates to "prodrugs" of the compounds (I). Thus, the claims 1 and 17 encompass compounds i.e. pharmaceutically acceptable biohydrolyzable derivatives, affinity reagents, and prodrugs having structures and formulae different from those compounds represented by formula (I). The said claims, however, do not give any clear indication to the structure or formulae of such derivatives/affinity reagents/prodrugs. Neither from the description nor from the claims it is apparent which structural features found in formula (I) must necessarily be present in said derivatives/affinity reagents/prodrugs, and which structural features may be varied. Therefore, the claims embrace compounds different from formula (I) without clearly defining the structure or formulae of such derivatives/ affinity reagents/prodrugs. Consequently, the scope of the claims 1 and 17 is unclear, contrary to the requirements of Article 6 PCT. In addition the difference between "pharmaceutically acceptable biohydrolyzable derivatives" and "prodrugs" is neither self-evident nor explained in the application, thereby adding to the unclarity of the claims.

5.3 Claim 18 relates to a process involving compounds (II) and (III) without, however, assigning the designation (II) and (III) to any individual formula. The claim is thus not clearly defined.

5.4 Claim 24 relates to a process involving inter alia 2-oxoindolines of the formula (VI). 2-Oxoindolines of the formula (VI), however, are not comprised within the claims from which claim 24 is defined as dependent, thereby resulting in a lack of clarity of the claim.

6 Further Deficiencies of the Application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art

disclosed in D1, D3 and D4 is not mentioned in the description, nor are these documents identified therein.